Review

MOLECULAR METABOLISM

Sex differences underlying pancreatic islet biology and its dysfunction

Maureen Gannon [1,2], **Rohit N. Kulkarni** [3,4,5], **Hubert M. Tse** [6,7], **Franck Mauvais-Jarvis** [8,9,*]

ABSTRACT

Background: The sex of an individual affects glucose homeostasis and the pathophysiology, incidence, and prevalence of diabetes as well as the response to therapy.

Scope of the review: This review focuses on clinical and experimental sex differences in islet cell biology and dysfunction during development and in adulthood in human and animal models. We discuss sex differences in β-cell and α-cell function, heterogeneity, and dysfunction. We cover sex differences in communication between gonads and islets and islet-cell immune interactions. Finally, we discuss sex differences in β-cell programming by nutrition and other environmental factors during pregnancy.

Major conclusions: Important sex differences exist in islet cell function and susceptibility to failure. These differences represent sex-related biological factors that can be harnessed for gender-based prevention of and therapy for diabetes.

Keywords Sex differences; Gender differences; Islet; β-cell; α-cell; Diabetes; Immune cells

1. INTRODUCTION

Sex differences in physiology begin early in development from the combination of genetic and hormonal cues and they continue after puberty [1]. These differences result from the combination of three major events: 1. The differences in the number and type of sex chromosomes; 2. The perinatal testosterone surges that masculinize the reproductive tract and the organization of neural circuits; and 3. The activity of gonadal hormones after puberty. The combination of these factors produces distinct male and female biological systems for islet cells *in vivo*.

Increasing evidence suggests that sex affects glucose homeostasis and the pathophysiology, incidence, and prevalence of diabetes, as well as response to therapy. Sex differences in glucose homeostasis and diabetes have been recently reviewed elsewhere [2–4]. Normoglycemic women have lower fasting plasma glucose concentrations than men and higher 2-h plasma glucose concentrations following an oral glucose tolerance test (OGTT) [5], slower gastric emptying [6], and higher insulin sensitivity than men [7]. In addition, in individuals with prediabetes, women tend to exhibit glucose intolerance, whereas men exhibit impaired fasting glucose [8]. This review will focus on clinical and experimental sex differences in islet biology and dysfunction during development and in adulthood. The study of sex differences in islet function and failure is of fundamental importance, because it will generate knowledge on sex-related biological factors that can be harnessed for better options for prevention of and therapy for diabetes.

2. SEX DIFFERENCES IN β-CELL FUNCTION UNDER NORMAL AND STRESS CONDITIONS

2.1. Clinical studies

Sex differences in β-cell function are apparent in clinical studies. Compared to healthy men and despite similar plasma glucose levels, healthy women exhibit enhanced postprandial plasma insulin and C-peptide concentrations after a meal [9], suggesting that women have increased insulin secretion for a given glucose load. In addition, the disposition index, which reflects insulin secretion for a given level of insulin action, is higher in women than in men, supporting greater insulin secretion in women [9]. In a recent study of 63 healthy Japanese men and women, the insulin responses to an oral glucose load were higher in females than males, with no differences in insulin sensitivity between the sexes [10]. Likewise, studies in older men and women suggest that for a given level of insulin action, women have higher levels of insulin secretion [11]. It has been hypothesized that the increased glucose-stimulated insulin secretion (GSIS) in females was due to sex differences in glucose-stimulated GLP-1 production. In the ADDITION-PRO study, a large study population of 1,462 Danish adults, normoglycemic women had a greater increase in serum GLP-1 concentrations following an OGTT, than normoglycemic men, even after adjusting for body weight, height or BMI [12]. This sex difference could be explained by the fact that the female hormone 17β-estradiol (E2) stimulates glucose-induced GLP-1 secretion as will be discussed below. However, the relationship between the increased serum GLP-1

[1]Department of Medicine, Vanderbilt University Medical Center, Nashville, USA [2]Department of Veterans Affairs, Tennessee Valley Health Authority, Nashville, TN, USA [3]Section of Islet Cell and Regenerative Biology, Joslin Diabetes Center, Boston, USA [4]Department of Medicine, Harvard Medical School, Boston, USA [5]Harvard Stem Cell Institute, Boston, MA, USA [6]Department of Microbiology, Birmingham, USA [7]Comprehensive Diabetes Center, University of Alabama at Birmingham School of Medicine, Birmingham, AL, USA [8]Department of Medicine, Section of Endocrinology and Metabolism, Tulane University Health Sciences Center School of Medicine, New Orleans, USA [9]Southeast Louisiana Veterans Healthcare System Medical Center, New Orleans, LA, USA

*Corresponding author. Tulane University Health Science Center, New Orleans, LA, USA. E-mail: fmauvais@tulane.edu (F. Mauvais-Jarvis).

Received May 22, 2018 • Accepted May 25, 2018 • Available online xxx

https://doi.org/10.1016/j.molmet.2018.05.017

following OGTT and the increased first phase insulin secretion was similar in men and women [12]. Therefore, sex differences in serum GLP-1 concentrations following OGTT do not seem to explain sex differences in β-cell function in humans. In the same cohort, individuals with prediabetes and type 2 diabetes (T2D) exhibited less of a GLP-1 increase than normoglycemic controls following an OGTT. This impaired serum GLP-1 increase in response to OGTT was most pronounced in women compared with men [12]. Thus, healthy women exhibit a greater increase in GLP-1 following an oral glucose challenge, but, as glucose tolerance deteriorates, this sex difference is no longer apparent. Interestingly, in individuals with prediabetes, women tend to be predisposed to impaired glucose tolerance, compared to men [8]. However, it is unknown if these phenotypic differences reflect differences in β-cell function.

Gender differences in β-cell failure are also observed in insulin-deficient forms of diabetes. For example, type 1 diabetes (T1D) is the only common autoimmune disease characterized by a male predominance [2–4,13]. Girls presenting with T1D in pubertal years have higher residual β-cell function than boys at diagnosis [14]. Similarly, ketosis-prone diabetes (KPD) is a phenotypically-defined form of T2D characterized by a strong male predominance (75%) and rapid β-cell failure leading to severe insulin deficiency [15]. In subjects with KPD, the male gender is associated with a more pronounced decrease in β-cell insulin secretory reserve, assessed by fasting and glucagon-stimulated C-peptide [16]. The rare women developing KPD were in an anovulatory state. Finally, a mutation in the β-cell transcription factor V-Maf avian musculoaponeurotic fibrosarcoma oncogene homolog A (MAFA), causes autosomal dominant inheritance of diabetes or insulinomatosis (insulin-secreting tumors of the pancreas causing adult-onset hyperinsulinemic hypoglycemia) with a sex dimorphism. Women with the MAFA mutation are more likely to develop insulinomatosis while men are more likely to develop diabetes [17]. The reason for this divergent phenotype has not yet been determined, but, interestingly, the women who developed insulinomatosis had a prior pregnancy, suggesting that the hormonal milieu of pregnancy influences the effect of this mutation on the β-cell.

2.2. Studies using human islets and β-cells

The Integrated Islet Distribution Program (IIDP; https://iidp.coh.org/) has greatly facilitated the use of cadaver donor human islets in research. Thus, we can now more easily assess whether intrinsic differences exist between islets and β cells obtained from male and female individuals. In one study, 53 male and 34 female human pancreatic islet donors were compared [18]. There were no significant differences in age, body mass index (BMI), hemoglobin A1c (HbA1c), islet purity or β-cell content between males and females. However, *ex vivo* GSIS was slightly higher in islets from females compared with males.

Information generated from studies of pancreas development and endocrine differentiation from multiple organisms has resulted in multistep directed-differentiation protocols that can convert human embryonic stem cells (hESCs) into pancreatic progenitor cells, which, several months following implantation into immunocompromised mice, develop into mature glucose-responsive insulin-secreting cells that are capable of reversing experimentally-induced diabetes [19,20]. To date, clinical trials assessing the utility of encapsulated hESC-derived pancreatic progenitors in patients with poorly controlled T1D have not been successful in regulating glycemia, likely due to fibrosis in the transplanted cells. Interestingly, recent studies suggest that the sex of the host into which hESC-derived pancreatic progenitors are transplanted may affect their ability to mature into optimally functional β-cells. Male and female mice were transplanted with two different stages of hESC-derived pancreatic cells: endocrine progenitors or insulin-positive cells. *In vivo* maturation of both cell populations into glucose-responsive insulin-secreting cells (as measured by circulating human C-peptide) was accelerated in female recipients (12 weeks compared to 16 weeks) compared with male hosts [21]. The authors concluded that E2 in female recipients promoted more rapid β-cell maturation. Indeed, a large body of evidence demonstrates that E2 protects rodent and human islets from multiple metabolic injuries [Reviewed in [22,23]], and E2 promotes human islet engraftment and revascularization in diabetic mice [24]. Interestingly, long-term (35 weeks) graft function was higher in male hosts compared to females, potentially due to increased adipose tissue associated with the grafts in females [21].

2.3. Studies using animal models

Most rodent studies examining effects of gene and/or environmental manipulations on β-cell mass and function have traditionally focused only on male adults given the stronger diabetic phenotype compared to females. This biased approach already reflects differences between the two sexes and has led to a paucity of data on sex differences in islet gene expression or β-cell function or whether islets from males and females react differently to stressors. However, recent evidence suggests that GSIS is modulated in a sex-specific manner by gonadal hormones. For example, testosterone enhances GSIS *in vivo* in male mice via action on the androgen receptor (AR) in β cells [25]. In cultured male mouse and human islets, testosterone binding an extranuclear AR enhances cAMP production and the insulinotropic effect of GLP-1. In contrast, in females, E2 increases glucose-induced GLP-1 secretion *in vivo* and GLP-1 secretion from primary cultures of mouse and human α cells and intestinal explants through the activation of estrogen receptors (ERs) [26]. Thus, although male and female mammals exhibit the same overall mechanism of nutrient-induced insulin secretion, the fine-tuning of insulin secretion is regulated in a sex-specific manner by sex hormones. GSIS in rodents declines significantly with age in both sexes [27,28]. However, isolated islets from female rats at 18 months of age still show higher glucose-stimulated insulin secretion (GSIS) *ex vivo* than those of males [27], confirming results obtained in humans [18]. Islets from elderly female rats showed elevated mitochondrial function (ATP content and oxygen consumption) compared with males when exposed to high glucose *ex vivo*. Mitochondrial biogenesis was also significantly higher in elderly female rats compared with males.

In multiple rodent models of diabetes in which β-cell failure is observed, there is also sex dimorphism. For instance, female animals are usually protected from development of the disease, with the exception of the NOD mouse as discussed in Section 4. Sexually dimorphic models including mice with streptozotocin-induced diabetes, the transgenic mouse overexpressing human islet amyloid polypeptide (hIAPP) in β cells, or the Zucker diabetic fatty (ZDF) rat have been reviewed elsewhere and will not be discussed in detail here [22,23]. These models, however, have been instrumental in revealing the role of sex in islet pathophysiology and have contributed to identifying the main female ovarian hormone 17β-estradiol (E2) as a critical factor in protecting human islets from metabolic injuries including oxidative stress, gluco-lipotoxicity, and apoptosis.

3. ISLET AND β-CELL HETEROGENEITY

Islet endocrine cell composition is known to vary according to the anatomical location within the pancreas and among different species

